Summary and general discussion
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Pregnancy and maternal weight change is the central theme of this thesis. Pregnancies, and especially those in which women gain weight excessively, are believed to contribute to weight retention, and the subsequent development or worsening of maternal overweight and obesity (1,2). In addition, excessive gestational weight gain contributes to an increased risk of complications for mother and child during pregnancy, delivery, neonatal life and to obesity in the offspring (3-11). The underlying question of this thesis is ‘how gestational weight gain can be influenced and the consequences thereof’.

What did we find?
Firstly in chapter 2 evidence was gathered on maternal nutrition in the Netherlands resulting in a narrative review. One of the conclusions was that no simple relationship exists between extra energy needs in pregnancy and extra energy intake advised, and that a universal ‘one size fits all’ advice regarding nutrition for well-nourished Dutch women cannot be justified. It might be better to give a personalized advice.

Subsequently, in the New Life(style), a randomized controlled trial (chapter 3), the effects were evaluated of individualized counseling regarding physical activity and nutrition in pregnancy on gestational weight gain and retention as the primary outcomes. The counseling intervention had neither an effect on gestational weight gain nor on weight retention at 52 weeks postpartum. In both the intervention and the control group, women had gained on average 11.3 kg from early to late pregnancy, and they were on average 1 kg lighter at 52 weeks postpartum compared to 15 weeks of pregnancy.

Because the counseling intervention had no measurable effect on gestational weight gain we further analysed the study population as a cohort and assessed in chapter 4, whether eating style, as well as behavioral determinants (i.e. attitude, social norm and self-efficacy) were of any significance for gestational weight gain. Interestingly, during pregnancy eating style was unstable in 34% of all women. At first sight emotional eaters gained more weight in pregnancy compared to restrained or external eaters. After hierarchical regression analyses none of the eating styles was associated with gestational weight gain.

Attitude, social norm, and self-efficacy were not of any significance on gestational weight gain.

Not only total weight gain is important, but also, from a public health perspective, what part of this weight gain is attributable to an increase in maternal adipose tissue. Also of importance is whether the increase in maternal adipose tissue is mostly of visceral or subcutaneous nature. In chapter 5 the concurrent validity was estimated between three different proxies of maternal adipose tissue: i.e. serum leptin, BMI and the sum of 4 skinfolds in pregnancy and the...
postpartum period. Because of the high correlation between the three methods, all methods seem to be equally suitable to estimate changes in maternal body fat during pregnancy and the year thereafter. However, none of the three methods is capable of differentiating between visceral or subcutaneous adipose tissue.

In chapter 6 we analyzed in a longitudinal cohort study the relationship between lifestyle factors and maternal weight change and pregnancy outcomes. Sedentary behavior, physical activity, sleeping patterns and BMI at 15 weeks of pregnancy were not related to gestational weight gain and pregnancy outcomes. Breastfeeding was not related to weight retention. Smoking during pregnancy was related to less weight retention (-5.1 kg) and lighter babies (-323 gram). We also found that many women quit smoking before getting pregnant (41% of 76), but that around 50% of them started again after having given birth. Some women (9%) lost >5% of their weight before getting pregnant, possibly preparing themselves to be fit for pregnancy. In our study the women who had lost weight, had more weight retention 52 weeks after delivery (4.9 kg) and delivered heavier babies (377 gram), compared to women with more stable weight before pregnancy. We cannot explain the latter finding, i.e. the heavier babies. The higher weight retention might be explained by a larger yo-yo effect in the women who had lost substantial weight before pregnancy. That is, they returned to their weight from before losing weight before pregnancy. These results show that one needs to extend the study period well beyond pregnancy (i.e. > 1 year) to study relationships between lifestyle factors and maternal weight change and pregnancy outcomes. Total physical activity (with moderate-to-vigorous intensity physical activity being part of this) and energy expenditure determine energy balance and therefore body weight. In chapter 7 we studied the relationship between moderate-to-vigorous intensity physical activity (MVPA) and body weight. Not surprisingly, we found that MVPA decreased during pregnancy. However, in our study MVPA was neither related to weight gain in pregnancy nor to weight retention. Perhaps such a relationship could not be established because the group of women had very low levels of MVPA. Another explanation could be that gestational weight gain cannot be influenced so easily, because of the physiological processes taking place during pregnancy overruling external stimuli.

It is known, mostly from training intervention studies, that PA has an effect on hormones related to energy homeostasis (12-14). Was there any effect of MVPA on these hormones in pregnancy in our study group? The only significant difference between women with levels of MVPA above the median, compared to women with MVPA below the median, was a lower fasting insulin and BMI at 15 weeks of gestation. At no other point in pregnancy or postpartum, significant differences were observed in hormonal markers between women with MVPA below or above the median for MVPA.
What did we learn?

In our study we approached the issue of pregnancy and maternal weight change from various perspectives.

Most studies reporting on gestational weight change restrict themselves to pregnancy. In our view, aside from weight change in pregnancy, weight change after and even before pregnancy is important as well. Gestational weight gain itself might not be that important for the development of maternal obesity and may be difficult to influence (15,16). Perhaps maternal weight gain during pregnancy is more ‘fixed’ in order to ensure fetal development, and cannot be changed much under ‘normal’ (body weight) conditions. The model for weight change of calories-in, calories-out in pregnancy might thus be too simple.

The mother’s metabolism is modified from the beginning of pregnancy, independent of lifestyle (17-19). It is known that during pregnancy the developing fetus demands more and more nutrients. The placenta increases the production of Growth Hormone (GH) and of Human Placental Lactogen (HPL) through pregnancy, leading to reduced insulin sensitivity and therefore, to increasing maternal glucose levels, which finally lead to an increase in the adipose tissue lipolytic activity (19). In the beginning the mother gains weight and maternal adipose tissue increases (20,21). Cholesterol and triglyceride levels increase also during pregnancy, with an increment in free fatty acids (FFAs) mostly near delivery (17-19). Those FFA may easily cross the placenta to guarantee a constant supply of nutrients for the fetus. Leptin, a hormone produced by white adipose tissue seems to be important in regulating nutrition and the energy-consuming processes of reproduction, pregnancy and lactation (22,23). In pregnancy, leptin sensitivity decreases and a state of leptin resistance develops resulting in a stimulation of food intake and maternal energy storage (24-27).

But apart from the maternal effects of leptin, leptin might play a role in the fetal programming via epigenetic variation (28,29).

The effect of maternal weight change during pregnancy on early-life programming of the fetus was not the topic of this thesis. We limited ourselves to birth weight. But in studies on fetal programming maternal weight dynamics even before conception in normal weight women play a role (30). It was reported that in normal weight women (BMI <25 kg/m) weight loss before pregnancy was associated with newborns small for gestational age and, independent of maternal BMI, a positive association was reported between weight loss before pregnancy and gestational diabetes and hypertension (30). In our study, however, the women who had lost weight before pregnancy, gave birth to significantly heavier babies (377 gram; 95% CI 94 to 661 gram).  

1 Epigenetics is mostly the study of heritable changes that are not caused by changes in the DNA sequence; to a lesser extent, epigenetics also describes the study of stable, long-term alterations in the transcriptional potential of a cell that are not necessarily heritable. Unlike simple genetics based on changes to the DNA sequence (the genotype), the changes in gene expression or cellular phenotype of epigenetics have other causes, thus use of the term epi- (Greek: ἐπί- over, outside of, around) -genetics. Ref Wikipedia.
The change in maternal energy homeostasis in pregnancy is of vital importance for the fetus and so it might not easily be influenced. Under extreme conditions, such as under- and over-nutrition, this change in energy homeostasis might be influenced, affecting the fetus (31,32). Whether the effect of under- and over-nutrition acts on the fetus via epigenetics by modifying energy homeostasis, maternal body weight gain or the amount and function of adipose tissue, is not clear at this point in time.

If maternal weight gain in pregnancy is more 'fixed' in order to ensure fetal development, and cannot be changed much under normal conditions, the importance of gestational weight gain related to obesity for the mother and her offspring is challenged. Perhaps nutritional status e.g. over- and underweight, of the mother before and during pregnancy might be even of more importance. This nutritional status might act on certain genes of the gamete or fetus, modifying their expression, so-called epigenetics (32-37). Differences in expression of genes may lead to differences in the development of fetal organs, including brain development, and to different crosstalk between fetal neurotransmitters involved in the energy homeostasis (38-44). These epigenetic changes might lead to a higher risk for developing obesity in the offspring (45,46).

Apart from weight change in pregnancy and nutritional status, maternal body composition as such might act on fetal programming (47). In the study of Kent, birth weight correlated positively with maternal fat-free mass and not with adiposity. The author suggested "that, in nondiabetic women, interventions intended to reduce fat mass during pregnancy may not prevent large-for-gestational-age neonates and revised guidelines for gestational weight gain in obese women may not prevent large-for-gestational-age neonates" (47).

Many scientists and health care providers consider pregnancy as "a window of opportunity" for the fetus and for introducing healthy behaviour to the mother (46,48,49). But if a change in health behaviour has been achieved it is not known how sustainable that change will be. For example changing addictive behaviour in pregnancy is sometimes successful by means of an intensive approach (49-52). In our study the limited sustainability of a behavioural change was illustrated by the fact that of the 31 women who stopped smoking in the year before getting pregnant, about half (16) started again after delivering their lighter baby's.

For that reason we should not limit the observation period regarding the effect of a lifestyle intervention to pregnancy alone. Lifestyle interventions and weight management should not just focus on pregnancy, but should be extended beyond pregnancy (53,54).

We have introduced measuring the effect of eating style in our study. Many studies on weight change mainly considered food intake and physical activity. But food intake (and thus energy intake) is related to determinants of food intake, such as eating style, attitude and self-esteem. When studying weight and weight changes, such determinants should be identified.
Knowledge on determinants might help to identify women at risk and can give guidance for intervention development.

**Methodological considerations**

Limitations to our study need to be discussed. First of all there is an issue with the sample. Healthy, relatively well-educated women with an average BMI of 23.7 participated in the New Lifestyle study, being capable of maintaining a healthy weight. This selective population may have given a selection bias.

The vast majority of the study population was Caucasian. As we know the prevalence of gestational diabetes is different in different ethnic groups. For example in the prevalence is higher in Hindustani Surinamese compared to Caucasian (55, 56).

Another limitation was the absolute number of women participating in the study and especially the small number of overweight or obese (BMI ≥ 25) women (21.4%). For instance, Hopkins hypothesized that in normal weight women, PA might not be associated with insulin sensitivity to ensure sufficient nutrients for the fetus, while this association might be present in obese pregnant women, with low insulin sensitivity already at the start of pregnancy and with abundant nutrients available (57).

Furthermore, we had neither objective data on energy intake nor objective data on prepregnancy body weight. Although misclassification of self-reported pre-pregnancy BMI is quite common (particularly women with a high BMI underreport their weight (58)), others have shown that in normal weight women, as in our study, self-reported BMI was quite valid (59,60).

**Implications for future research**

Efforts to influence maternal weight have been numerous, because abnormal weight change is associated with maternal and fetal morbidity and even mortality. But gestational weight gain cannot be influenced so easily and if limiting gestational weight gain will result in better pregnancy and weight outcomes over the long term is not clear at the moment (15,16).

Special attention should be paid to the effect of maternal weight dynamics even outside pregnancy on maternal weight development, but also on early-life programming (30). And not only weight change, but also maternal body composition should be a part of those RCT’s (47). The role of obesity of the father is as yet an unexplored field of study. Recent studies suggested a preconceptional impact of paternal obesity on the epigenetics of the offspring during spermatogenesis (61,62). The effect of maternal obesity on oogenesis is even more unexplored. Therefore, more research is needed on the effect of weight dynamics of both parents on the fetal development and on how expression of genes in the offspring is influenced. Since we know that obesity is also a social disease, as visualized in a large social network in the Framingham study, only focusing on pregnant women and their gestational weight gain without involving their spouses and even families might not be the most successful way to stop the obesity epidemic (63).
Based on the above, we recommend to get more insight into the effects of body weight management by conducting RCT’s that assess the long-lasting effects of weight management during and beyond pregnancy on maternal and neonatal health and especially focus on underweight and overweight or obese women. In these RCT’s, the social network (spouse, family, friends) need to be involved.

**Implications for clinical practice**

Many uncertainties still exist: the effect of adjusting gestational weight gain according existing guidelines for different weight categories of women; the effect of the timing and the amount of weight loss before getting pregnant and the effect of this weight loss on mother and child; the importance of maternal body composition and the contribution of the father on maternal obesity and obesity of the offspring.

Based on our results we have no specific recommendations on this topic, but some general recommendations can be given.

Counselling on healthy weight and physical activity should take place not only during, but, more importantly, before and after pregnancy. If women already experience weight problems before trying to conceive, body weight counselling should be commenced.

Obese women however, should be encouraged to loose weight long before they try to conceive. Based on our study women should loose weight at least more than 6 months before trying to conceive.

**Personal view**

In this thesis, pregnancy and maternal weight change is the central theme.

The question I wanted to answer was whether nature or nurture (64-66) influenced maternal weight in pregnancy. A bit naïve perhaps as reality seems to be more complicated. Maternal weight change seems to be more difficult to influence. Short and long term effects must be studied comprehensively. Quoting Traynor “The old dogma of nature versus nurture is dead, but unfortunately it has been replaced by a puzzle even harder to solve” (67).